EFFECT OF ANTIMALARIAL DRUGS ON HUMAN MONONUCLEAR CELL RESPONSE TO MITOGENIC LECTINS

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OBJECTIVE : To evaluate the effect of mefloquine and halofantrine on human mononuclear cell (MNC) response to mitogenic lectins.

BACKGROUND : Mitogenic lectin induced MNC blast transformation provides an established assay for evaluation of cellular immune responsiveness (1). The purpose this study is to use the mitogenic lectin *in vitro* assay to assess whether the new antimalarial drugs, mefloquine and halofantrine, suppress cellular immune responsiveness in human MNC.

Mefloquine and quinine have been shown to suppress mitogenic response to lectins by mouse MNC (2, 3). There are no published studies on whether halofantrine effects MNC responsiveness.

Since immunosuppression is a characteristic of malaria infection the possibility that an antimalarial agent may itself compromise immune responsiveness becomes an important clinical consideration. A drug induced decrease in host immune capacity during malaria infection could result in a prolonged parasite clearance time and subsequent delayed recovery from the disease. Similarily, the compromise to the patient may result in increased susceptibility to intercurrent illness. There is also the concern for malaria endemic populations where suboptimal chemoprophylaxis may combine with the disease itself so as to compromise vaccine employment - especially a prospective malaria vaccine.

METHODS : *Mononuclear Cell (MNC) Isolation.* Peripheral blood MNC were isolated from heparinized whole blood by diluting the blood 1:2 in Hanks balanced salt solution followed by Ficoll-Hypaque centrifugaiton (4).

MNC Mitogenic-lectin Assay. A method for assay of lectin-induced blast transformation has been established in our laboratory (5). Cultures were done in triplicate. The stimulation index (SI) was determined based on the means of triplicate assays according to the following formula: SI = (CPM from stimulated cultures/CPM from nonstimulated cultures) and Δ CPM (CPM from stimulated culture - CPM from nonstimulated cultures).

RESULTS : *Effect of Halofantrine on Responsiveness of MNC from Normal Donors and Malaria Patients to Concanavalin A.* Table 1 shows that Concanavalin A (CON A) stimulation of MNC from normal donors in the presence of halofantrine (10^{-3} - 10^{-8} M) was suppressed. Data are presented as percent of control for the stimulation index (SI) where the control SI represents responsiveness to CON A in the absence of halofantrine exposure. In patients with malaria infection (Table 2) the MNC response to CON A was also suppressed. There was no apparent significant difference in the level of suppression due to halofantrine when donors were compared to individuals with malaria infection.

Effect of Mefloquine on Responsiveness of MNC from Normal Donors and Malaria Patients to Concanavalin A. Table 3 shows that Concanavalin A (CON A) stimulation of MNC from normal donors in the presence of mefloquine (10^{-3} - 10^{-8} M) was suppressed. Table 4 shows that in patients with malaria infection the MNC response to CON A was likewise suppressed. The level of MNC suppression due to mefloquine was comparable for both malaria infected individuals and donors.

Both halofantrine and mefloquine appear to suppress MNC response to CON A stimulation *in vitro*. The level of suppression is comparable for both drugs.

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Table 1. Effect of Halofantrine on Responsiveness of MNC from Normal Donors to Concanavalin A.

Halofantrine (Molar concentration)	Donor MNC Stimulation Index (% of control)			
	A	B	C	D
10^{-3} M	0	7	0	3
10^{-4} M	23	24	31	8
10^{-5} M	14	24	21	27
10^{-6} M	20	25	53	16
10^{-7} M	14	19	40	22
10^{-8} M	25	26	61	20

Table 2. Effect of Halofantrine on Responsiveness of MNC from Malaria Patients to Concanavalin A.

Halofantrine (Molar concentration)	Patient MNC Stimulation index (% of control)			
	A*	B*	C*	D*
10^{-3} M	16	3	0	0
10^{-4} M	16	18	41	11
10^{-5} M	25	16	63	13
10^{-6} M	21	20	81	30
10^{-7} M	22	14	58	31
10^{-8} M	23	28	71	25

* *P. falciparum* infection

** *P. vivax* infection

Table 3. Effect of Mefloquine on Responsiveness of MNC from Normal Donors to Concanavalin A.

Mefloquine (Molar concentration)	Donor MNC Stimulation index (% of control)			
	A	B	C	D
10^{-3} M	0	0	2	0
10^{-4} M	4	3	2	0
10^{-5} M	10	32	9	10
10^{-6} M	18	23	7	16
10^{-7} M	18	32	27	17
10^{-8} M	17	18	25	27

Table 4. Effect of Mefloquine on Responsiveness of MNC from Malaria Patients to Concanavalin A.

Mefloquine (Molar concentratipn)	Patient MNC Stimulation index (% of control)			
	A*	B*	C*	D*
10^{-3} M	1	1	0	2
10^{-4} M	1	0	0	0
10^{-5} M	8	28	43	9
10^{-6} M	7	31	21	23
10^{-7} M	7	25	13	35
10^{-8} M	14	24	17	55

* *P. falciparum* infection

** *P. vivax* infection